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10/544,146	05/05/2006	Shyam S. Mohapatra	USF:T193XC1	9945
23557 7590 04/19/2010 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614				
EXAMINER SCHNIZER, RICHARD A				
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary

Application No.

10/544,146

Applicant(s)

MOHAPATRA ET AL.

Examiner

Richard Schnizer

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-52-59, 61, 62, 64-67 and 69-81 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42, 52-55, 57-59, 61, 62, 64-67, 69-77, and 79-81 is/are rejected.
- 7) ☒ Claim(s) 56 and 78 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-944)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/24/10
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

An amendment was received and entered on 2/24/10.

Claims 79-81 were added.

Claims 42, 52-59, 61, 62, 64-67, and 69-81 are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 42, 52-55, 58, 59, 64, 69, 71-73, 75-77, 79, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

Iverson taught methods of inhibiting Dengue virus replication in a human by intravenous administration of an antisense oligonucleotide directed against the Dengue genome. See abstract and paragraphs 34, 36, 40, 50, 153, 154, 158, Example 3, and claim 16.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the portion of the RNA encoding the structural proteins, and the 3' end of the virus genome.

Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. One oligonucleotide was directed to a target sequence common to all four DV serotypes. Two oligonucleotides were directed to a non-structural protein (ns5a). See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus structural gene prM RNA, and its use to inhibit DV infection by administration to mosquito cells in vitro. See abstract.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in and viral vectors. See last paragraph on page 6052.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

It was clear to those of ordinary skill in the art at the time of the invention that there was interest in inhibiting DV replication in human cells, particularly in view of the teachings of Iversen and Raviprakash, and that RNA interference represented an alternative to antisense methods of gene suppression. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Iversen by substituting an expression vector encoding an shRNA directed against DV for the antisense oligonucleotide of Iversen. One would have been

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motivated to do so in order to obtain the advantages disclosed by Tuschl. One of ordinary skill appreciates that shRNAs operate through the same pathway as siRNAs, and would reasonably expect shRNAs to deliver performance superior to that obtained using antisense in view of the teachings of Tuschl. One would have had a reasonable expectation of success because the technology for expressing shRNAs in mammalian cells was available prior to the time of the invention (see Yu above), and there was no reason to doubt that it would have functioned in vivo in human cells.

It would have been similarly obvious to target any of the DV genomic RNA regions set forth by Iversen, Raviprakash, or Adelman because the genome of DV is a positive strand RNA encoding a single polyprotein, such that cleavage of any of the targets would have been expected to inhibit DV replication, particularly those at the 5' genome end, e.g. those directed against prM. One would have been motivated to include expression cassettes for more than one siRNA in order to increase the level of inhibition achieved.

With regard to whether or not the siRNA vector is administered prior to or after DV infection, Iversen taught that treatment could be either prophylactic or post-infection (paragraph 71). In any case, an infected individual will produce infectious virus such that treatment of an infected individual would be considered to result in the treatment of cells that had not yet become infected, but would become infected subsequent to treatment.

Absent evidence to the contrary, delivery to dendritic cells is considered to be inherent in intravenous administration.

Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, 75-77, 79, and 81 above, and further in view of Yu et al (US 6852528).

The teachings of Iverson, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

These references do not teach a vector conjugated with chitosan. However, one of ordinary skill appreciates that there is a wide variety of gene delivery techniques which one may employ interchangeably as a matter of design choice. Among these are microinjection (the method used by Raviprakash), lipofection (used by Adelman (2002) and Yu (2002)). Yu ('528) also taught that a variety of methods could be used to deliver nucleic acids to cells including microparticle formation with polycations such as chitosan-based compounds, as well as liposome-mediated transfection and microinjection. See column 22, lines 17-44; column 23, lines 30-47; and column 31, lines 22-38. It would have been obvious to one of ordinary skill in the art to select any of these commonly used transfection techniques, as they were all well recognized in the art as exchangeable alternatives.

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, 75-77, 79, and 81 above, and further in view of Kumar et al (US 7067633).

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

These references do not teach a vector comprising a tissue-specific or inducible promoter.

One of ordinary skill in the art recognizes that particular promoters are selected as a matter of design choice. Inducible and tissue-specific promoters allow one to control the expression of a given construct either through the type of cell used or through the presence or absence of an inducer. For example, Kumar taught that it is important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type, organelle, and organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters enhancers, and cell type combinations for protein expression. Various promoters employed may be constitutive, tissue specific, inducible and/or useful under the appropriate conditions to direct high level expression of the introduced DNA segment. It would have been obvious to one of ordinary skill in the art to select any of these

commonly used promoters based on the need to control expression as a matter of design choice.

Claims 65-67, and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iverson et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52-55, 58, 59, 64, 69, 71-73, 75-77, 79, and 81 above, and further in view of Hope et al (US Patent 6,136,597)

The teachings of Iverson, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

The cited references did not teach adeno-associated virus vectors.

Hope taught that expression cassettes could be delivered by a variety of viral or non-viral vectors, including plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of

prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above. The structural characteristics of the AAV vector of Hope are indistinguishable from those recited in the instant claims, so the functional characteristic of not causing acute inflammation in dendritic cells is considered to be inherent.

Claims 72, 73, 75, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Libraty et al (J. Virol 75(8): 3501-3508, 2001), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

Libraty disclosed dendritic cells infected by DV, and indicated that these cells were relevant to understanding the pathogenesis of DV and the development of therapeutic strategies. See abstract.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the portion of the RNA encoding the structural proteins, and the 3' end of the virus genome. Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. One oligonucleotide was directed to a target sequence common to all four DV serotypes. Two were directed to a non-structural protein (ns5a). See abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Adelman taught a plasmid vector encoding a inverted repeat siRNA directed against Dengue virus prM RNA, and its use to inhibit DV infection. See abstract. Adelman indicated that expression from a Sindbis vector of RNA with antisense polarity and that of RNA with sense polarity were equally effective to induce resistance to DEN-2 in mosquito cells and adult mosquitoes, noting that virus resistance had many of the characteristics of RNA silencing, including the presence of Dengue virus-specific siRNA.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in viral vectors. See last paragraph on page 6052

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cells of Libraty in the experiments of Raviprakash, because Libraty taught that these cells were relevant to understanding the pathogenesis of DV and the development of therapeutic strategies. One of ordinary skill appreciates that gene expression inhibition studies can shed light on the pathogenesis of DV as well as provide information that would be considered useful in the development of therapies, such as for determining the best genomic target region. It would have been similarly obvious to modify the experiments of Raviprakash to use siRNA expression vectors, such as those taught by Adelman or Yu, instead of antisense oligonucleotides. One

would have been motivated to do so in order to obtain the advantages disclosed by Tuschl. One of ordinary skill appreciates that shRNAs operate through the same pathway as siRNAs, and would reasonably expect shRNAs to deliver performance superior to that obtained using antisense in view of the teachings of Tuschl. One would have had a reasonable expectation of success because the technology for expressing shRNAs in mammalian cells was available prior to the time of the invention (see Yu above), and there was no reason to doubt that it would have functioned in human dendritic cells. It would have been similarly obvious to target any of the DV genomic RNA regions set forth by Raviprakash or Adelman because genome of DV is a positive strand RNA encoding a single polypeptide, such that cleavage of any of the targets would have been expected to inhibit DV replication, particularly those at the 5' genome end, e.g. those directed against prM.

Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over Libraty et al (J. Virol 75(8): 3501-3508, 2001), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 72, 73, 75, and 77 above, and further in view of Hope et al (US Patent 6,136,597).

The teachings of Libraty, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in human blood dendritic cells by administration of a vector encoding an shRNA directed against DV RNA.

The cited references did not teach adeno-associated virus vectors.

Hope taught that expression cassettes could be delivered by a variety of viral or non-viral vectors, including plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above. The structural characteristics of the AAV vector of Hope are indistinguishable from those recited in the instant claims, so the functional characteristic of not causing acute inflammation in dendritic cells is considered to be inherent.

Response to Arguments

Applicant's arguments filed 2/24/10 have been fully considered but they are not persuasive.

Applicant asserts that the claimed invention is non-obvious because the combined references did not provide one of ordinary skill in the art at the time of the

invention with a reasonable expectation of successfully inhibiting the expression of Dengue virus genes within a human host suffering from Dengue virus infection. Applicant relies for support on Subramanya et al (2010, of record) who indicated that non-selective transfection methods may not work well for primary hematopoietic cells such as DCs. Applicant asserts that the important step of developing a method to introduce Dengue virus-targeted siRNA into DCs to inhibit viral replication was first achieved by the instant inventors, pointing to Examples 8 and 9 of the instant specification which show that adeno associated virus vectors can transduce DCs, and encoded siRNAs can inhibit subsequent DV infection and DV-induced apoptosis in DCs. Applicant further asserts that none of the cited references shows nucleic acid delivery to DCs, and concludes that the combined references did not provide one of ordinary skill in the art at the time of the invention with a reasonable expectation of success.

Applicant's arguments are unpersuasive because they are based entirely on the issue of the predictability of transfecting DCs, but do not address the predictability of transfecting other DV targets, such as hepatocytes and macrophages. Note that only claim 75 explicitly requires transfection of DCs, and claim 69 appears to indirectly require DC transfection. None of the other claims requires transfection of DC cells. An et al (Virology 23: 70-77, 1999, of record) provided evidence that DV could infect hepatocytes and replicate therein (see abstract and discussion). Applicant has presented no evidence or argument that one of ordinary skill at the time of the invention would not have reasonably expected to be able to deliver siRNA to DV-infected hepatocytes in vivo. Applicant has indicated previously that DV infects and replicates in

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macrophages (Applicant's Remarks filed 10/27/08 at page 5, penultimate sentence of second full paragraph), and this position is supported by Subramanya (see abstract). However, Applicant has presented no evidence or argument that one of skill in the art at the time of the invention could not have accomplished delivery to macrophages in vivo with a reasonable expectation of success using the methods of the combined references.

Applicant's arguments with specific regard to the unpredictable nature of transfecting DCs are also unpersuasive. While, Subramanya indicated that non-selective transfection methods may not work well for primary hematopoietic cells, this does not necessarily mean that one of ordinary skill would not have had a reasonable expectation of successfully combining the cited references to arrive at the claimed invention. To circumvent the potential problem of non-selective transfection methods not working well for DCs, Subramanya developed a vector that targeted DCs through the use of a peptide shown to bind DCs specifically. This does not mean that those of ordinary skill in the art at the time of the invention believed that DCs could not be transfected in the absence of such a vector. Applicant has presented no clear evidence that one of ordinary skill would have doubted that at least some DCs would have been transfected by the methods of the combined references, and that DV gene expression would have been inhibited in those transfected cells. On the other hand, the prior art showed that DCs could be transfected in vivo. Palmowski et al (J. Immunol. 172: 1582-1587, 2004) demonstrated that dendritic cells could be directly transfected in vivo by intravenous administration of lentiviral vectors. See also the following references which

disclose in vivo transfection of DCs: Condon et al (Nature Medicine 2(10): 1122-1128, 1996), Song et al (Proc. Nat. Acad. Sci. USA 94: 1943-1948, 1997), Porgador et al (J. Exp. Med. 188(6): 1075-1082, 1998), Barratt-Boyces (J. Immunol. 164: 2487-2495, 2000), and Larregina et al (Gene Therapy 8: 608-617, 2001). These references are not relied upon for the rejection itself, but are provided as a courtesy to Applicant merely to show that those of ordinary skill at the time of the invention would have been well aware that DCs could have been transfected with expression vectors in vivo. Accordingly Applicant's arguments that there would not have been a reasonable expectation of success are unpersuasive and the rejections are maintained.

Conclusion

No claim is allowed.

Claims 56 and 78 are objected to because they depend from rejected claims, but would be allowable if rewritten in independent form with all of the limitations of the claims from which they depend.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Fereydown Sajjadi, can be reached at (571) 272-3311. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635